

200-126 68007 1803  
Atty Dkt 246102002700  
Client ID: 157  
PATENT



I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on 3/11/93

3/11/93  
Date

Signature

RECEIVED  
APR 02 1993  
GROUP 1800

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

CHRIS BUHR et al.

Serial No.: 07/652,978

Group Art Unit: 1803

Filing Date: February 8, 1991

Examiner: G. Kunz

Title: METHYLENE PHOSPHONATE  
OLIGONUCLEOTIDE ANALOGS  
AND OLIGONUCLEOTIDE  
ANALOGS MADE THEREFROM

THIRD SUPPLEMENTAL  
INFORMATION DISCLOSURE STATEMENT

The Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Dear Sir:

The information listed below may be material to the  
Examination of this application.

The following were listed on pages 31-34 of the present  
application and not previously cited to the Office in the  
application:

Stein, et al., "Oligodeoxynucleotides as Inhibitors of  
Gene Expression: A Review," Cancer Res., 48:2659-2688  
(1988)

060 MC 03/30/93 07652978

1 126 200.00 CK

-1-

2461027.3DS

van der Krol, et al., "Modulation of Eukaryotic Gene Expression by Complementary RNA or DNA Sequences," BioTechniques, 6:958-976 (1988)

Weintraub, H.M., "Antisense RNA and DNA," Scientific American, 40-46 (January 1990)

Goodchild, J., "Inhibition of Gene Expression by Oligonucleotides," Oligodeoxynucleotides: Antisense Inhibitors of Gene Expression, chapter 3 (J.S. Cohen, ed.) 1989, CRC Press, Boca Raton, Florida.

Dervan, P.B., "Oligonucleotide Recognition of Double-helical DNA by Triple-helix Formation," Oligodeoxynucleotides: Antisense Inhibitors of Gene Expression, chapter 9 (J.S. Cohen, ed.) 1989, CRC Press, Boca Raton, Florida

Dervan, P.B., "Sequence Specific Recognition of Double Helical DNA. A Synthetic Approach," Nucleic Acids and Molecular Biology, volume 2, pp. 49-64 (F. Eckstein and D.M.J. Lilley, eds.) 1988, Springer-Verlag, Berlin

Zon, G., "Oligonucleotide Analogues as Potential Chemotherapeutic Agents," Pharmaceutical Res. 5:539-549 (1988)

Stein et al., "Phosphorothioate Oligodeoxynucleotide Analogues," Oligodeoxynucleotides: Antisense Inhibitors of Gene Expression, chapter 5 (J.S. Cohen, ed.) 1989, CRC Press, Boca Raton, Florida

Caruthers, M.H., "Synthesis of Oligonucleotides and Oligonucleotide Analogues," Oligodeoxynucleotides:

Antisense Inhibitors of Gene Expression, chapter 1,  
(J.S. Cohen, ed.) 1989, CRC Press, Boca Raton, Florida.

Grandas, et al., "Synthesis of Deoxycytidine Oligomers  
Containing Phosphorodithioate Linkages," Tetrahedron  
Lett. 30(5):543-546 (1989)

Brill, et al., "Synthesis of Oligodeoxynucleoside  
Phosphorodithioates via Thioamidites," J. Amer. Chem.  
Soc. 111:2321-2322 (1989)

Caruthers, et al., "Synthesis and Biological Studies  
with Dithioate DNA," 9th International Round Table:  
Nucleosides, Nucleotides, and their Biological  
Applications (July 30-August 3, 1990) Uppsala, Sweden

Miller, P.S., "Non-ionic Antisense Oligonucleotides,"  
Oligodeoxynucleotides: Antisense Inhibitors of Gene  
Expression," chapter 4 (J.S. Cohen, ed.) 1989, CRC  
Press, Boca Raton, Florida

Engel, R., "Phosphonates as Analogues of Natural  
Phosphates," Chem. Rev. 77:349-367 (1977)

Mikhailov, et al., "Use of 5-Deoxy-ribo-Hexofuranose  
Derivatives for the Preparation of 5'-Nucleotide  
Phosphonates and Homoribonucleosides," Collect. Czech.  
Chem. Commun., 54:1055-1067 (1989)

Martin, et al., "Synthesis of 4'-  
Hydroxymethyl)Guanosine and a Phosphonate Analogue of  
Guanylic Acid," Nucleosides and Nucleotides,  
7(3):365-374 (1988)

Hampton, et al., "Synthesis of Homoadenosine-6'-phosphonic Acid and Studies of Its Substrate and Inhibitor Properties with Adenosine Monophosphate Utilizing Enzymes," Biochemistry, 12:1730-1736 (1973)

Hampton, et al., "Synthesis of 6'-Cyano-6'-deoxyhomoadenosine-6'-phosphonic Acid and Its Phosphoryl and Pyrophosphoryl Anhydrides and Studies of Their Interactions with Adenine Nucleotide Utilizing Enzymes," Amer. Chem. Soc., 95(13):4404-4414 (1973)

Montgomery, et al., "The Use of the Wittig Reaction in the Modification of Purine Nucleosides," J. Het. Chem., 11:211-218 (1974)

Hampton, et al., "Design of Substrate-Site-Directed Irreversible Inhibitors of Adenosine 5'-Phosphate Aminohydrolase. Effect of Substrate Substituents on Affinity for the Substrate Site." J. Med. Chem., 19(8):1029-1033 (1976)

Hampton, et al., "Design of Substrate-Site-Directed Inhibitors of Adenylate Kinase and Hexokinase. Effect of Substrate Substituents on Affinity for the Adenine Nucleotide Sites," J. Med. Chem., 19:1371-1377 (1976)

Kappler, et al., "Isozyme-Specific Enzyme Inhibitors. 10. Adenosine 5'-Triphosphate Derivatives as Substrates or Inhibitors of Methionine Adenosyltransferases of Rat Normal and Hepatome Tissues," J. Med. Chem., 29:318-322 (1986)

Fuertes, et al., "Synthesis and Enzymatic Activity of 1,2,4-Triazole-3-carboxamide 6'-

Deoxyhomoribonucleoside-6'-phosphonic Acid and Related  
Compounds," J. Med. Chem., 17(6):642-645 (1974)

Marquez, et al., "Thiazole-4-carboxamide Adenine  
Dinucleotide (TAD). Analogues Stable to  
Phosphodiesterase Hydrolysis," J. Med. Chem.,  
29:1726-1731 (1986)

Albrecht, et al., "Homonucleoside Phosphonic Acids,"  
Tetrahedron, 40(1):79-85 (1984)

Mazur, A., et al., "Isosteres of Natural Phosphates.  
11. Synthesis of a Phosphonic Acid Analogue of an  
Oligonucleotide," Tetrahedron, 40(20):3949-3956 (1984)

Barton, et al., "Stereoselectivity in Radical Reactions  
of 2'-Deoxynucleosides. A Synthesis of an Isostere of  
3'-azido-3'-deoxythymidine-5'-monophosphate,"  
Tetrahedron Lett., 30(37):4969-4972 (1989)

Tanaka, et al., "Cleavage of a Nucleosidic Oxetane with  
Carbanions: Synthesis of a Highly Promising Candidate  
for Anti-HIV Agents -- A Phosphonate Isostere of ACT  
5'-Phosphate," Tetrahedron Lett., 30(19):2567-2570  
(1989)

Montgomery, et al., "Phosphonate Analogue of 2'-Deoxy-  
5-fluorouridylic Acid," J. Med. Chem., 22(1):109-111  
(1979)

Griffin, et al., "Nuclear Magnetic Resonance Studies of  
a Ribonuclease-Dinucleoside Phosphonate Complex and  
Their Implications for the Mechanism of the Enzyme,"  
Annals New York Academy of Sciences, 222:693-708 (1978)

Kaplan, et al., "DNA Synthesis on Solid Supports and Automation," Synthesis and Applications of DNA and RNA, chapter 2 (S.A. Narang, ed.) 1987, Academic Press, Orlando, Florida.

Crockett, G.C., "The Chemical Synthesis of DNA," Aldrichimica Acta, 16:47-55 (1983)

Agarwal, et al., "Chemical Synthesis of Polynucleotides," Angew. Chem. internat. Edit., 11(6):451-459 (1972)

Sproat, et al., "Solid-phase Synthesis of Oligodeoxyribonucleotides by the Phosphotriester Method," Oligonucleotide Synthesis: A Practical Approach, chapter 4 (M.J. Gait, ed.) 1984, IRL Press, Oxford, England

Prisbe, et al., "Synthesis and Antiherpes Virus Activity of Phosphate and Phosphonate Derivatives of 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine," J. Med. Chem., 29:671-675 (1986)

Duke, et al., "In vitro and in vivo activities of phosphate derivatives of 9-(1,3-dihydroxy-2-propoxymethyl)-guanine against cytomegaloviruses," Antiviral Research, 6:299-308 (1986)

Reist, et al., "Synthesis of Phosphonic Acid Analogs of Acyclovir (ACV) and Ganciclovir (DHPG)," Nucleosides and Nucleotides, 8:919-922 (1989)

Sidwell, et al., "Effect of Phosphonic Acid Analogs of Acyclovir and Ganciclovir on in vitro cytomegalovirus

Watanabe, et al., "Nucleosides. 110. Synthesis and Antiherpes Virus Activity of Some 2'-Fluoro-2'-deoxyarabinofuranosylpyrimidine Nucleosides," J. Med. Chem., 22(1):21-24 (1979)

Tann, et al., "Fluorocarbohydrates in Synthesis. An Efficient Synthesis of 1-(2-Deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)-5-iodouracil ( $\beta$ -FIAU) and 1-(2-Deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)thymine ( $\beta$ -FMAU)," J. Org. Chem., 50:3644-3647 (1985)

Howell, et al., "Antiviral Nucleosides. A Stereospecific, Total Synthesis of 2'-Fluoro-2'-deoxy- $\beta$ -D-arabinofuranosyl Nucleosides," J. Org. Chem., 53:85-88 (1988)

van de Sande, et al., "Parallel Stranded DNA," Science, 241:551-557 (1988)

Atkinson, et al., "Solid-phase Synthesis of Oligodeoxyribonucleotides by the Phosphite-triester Method," Oligonucleotide Synthesis: A Practical Approach, chapter 3, (M.J. Gait, ed.) 1984, IRL Press Limited, Oxford, England

de Vries, et al., "Inhibition of the growth of *Plasmodium falciparum* and *Plasmodium berghei* by the DNA polymerase inhibitor HPMPA," Mol. Biochem. Parasitol., 47:43-50 (1991)

Antineoplastic Agents, p. 127-165, (W.A. Remers, ed.) 1984, Wiley & Sons, New York.

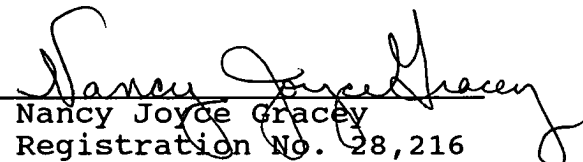
Sterzycki, et al., "Synthesis and Anti-HIV Activity of  
Several 2'-Fluoro-Containing Pyrimidine Nucleosides,"  
J. Med. Chem., 33:2150-2157 (1990)

Borthwick, et al., "Fluorocarbo-cyclic Nucleosides:  
Synthesis and Antiviral Activity of 2'- and 6'-  
Fluorocarbo-cyclic 2'-Deoxy Guanosines," J. Med. Chem.,  
34:907-914 (1991)

Applicants would appreciate the Examiner initialling  
and returning the Form PTO-1449, indicating that the  
references have indeed been considered and made of record  
herein.

A check for \$200 for filing this IDS is enclosed.

Respectfully submitted,

By:   
Nancy Joyce Gracey  
Registration No. 28,216

MORRISON & FOERSTER  
755 Page Mill Road  
Palo Alto, California 94304-1018  
(415) 677-6332  
Fax: (415) 677-6404

Attachment: Form-1449 and copies of documents listed  
thereon



infections," Nucleosides and Nucleotides, 8:833-836  
(1989)

Still, et al., "Rapid Chromatographic Technique for  
Preparative Separations with Moderate Resolution," J.  
Org. Chem., 43:2923-2925 (1978)

Jones, R., Oligonucleotide Synthesis: A Practical  
Approach, chapter 3, pp. 25-27 (M.J. Gait, ed.) 1984,  
IRL Press Limited, Oxford, England

Jones, R., "Protection of the 5'-Hydroxyl Group as a  
4,4'-Dimethoxytrityl Ether," Oligonucleotide Synthesis:  
A Practical Approach, chapter 4.1, pp. 27-28 (M.J.  
Gait, ed.) 1984, IRL Press Limited, Oxford, England.

Jones, et al., "A New Stable Wittig Reagent Suitable  
for the Synthesis of  $\alpha,\beta$ -Unsaturated Phosphonates,"  
Tetrahedron Lett., 55:5731-34 (1968)

Cusack, et al., "2,4,6-Tri-Isopropylbenzenesulphonyl  
Hydrazide: A Convenient Source of Di-imide,"  
Tetrahedron, 32:2157-62 (1976)

ElAmin, et al., "Removal of Benzyl-type Protecting  
Groups from Peptides by Catalytic Transfer  
Hydrogenation with Formic Acid," J. Org. Chem.,  
44(19):3442-3444 (1979)

Chu, et al., "Nucleosides. CXXXV. Synthesis of Some 9-  
(2-Deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)-9H-purines and  
Their Biological Activities," Chem. Pharm. Bull.,  
37(2):336-339 (1989)